



# The Dose-Response Relationship Between Body Mass Index and the Risk of Incident Stage $\geq 3$ Chronic Kidney Disease in a General Japanese Population: The Ibaraki Prefectural Health Study (IPHS)

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Received January 30, 2014; accepted April 25, 2014; released online July 5, 2014

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## ABSTRACT

**Purpose:** To examine the relationship between body mass index (BMI) and the risk of stage  $\geq 3$  chronic kidney disease (CKD) in a general Japanese population.

**Methods:** A total of 105 611 participants aged 40–79 years who completed health checkups in Ibaraki Prefecture, Japan, and were free of CKD in 1993 were followed-up through 2006. Stage  $\geq 3$  CKD was defined by an estimated glomerular filtration rate  $< 60$  mL/min/1.73 m<sup>2</sup> reported during at least 2 successive annual surveys or as treatment for kidney disease. Hazard ratios (HRs) for the development of stage  $\geq 3$  CKD relative to the BMI categories were calculated using the Cox proportional hazards regression model, which was adjusted for possible confounders and mediators.

**Results:** During a mean follow-up of 5 years, 19 384 participants (18.4%) developed stage  $\geq 3$  CKD. Compared to a BMI of 21.0–22.9 kg/m<sup>2</sup>, elevated multivariable-adjusted HRs were observed among men with a BMI  $\geq 23.0$  kg/m<sup>2</sup> and women with a BMI  $\geq 27.0$  kg/m<sup>2</sup>. Significant dose-response relationships between BMI and the incidence of stage  $\geq 3$  CKD were observed in both sexes ( $P$  for trend  $< 0.001$ ).

**Conclusions:** Obesity was associated with the risk of developing stage  $\geq 3$  CKD among men and women.

**Key words:** chronic kidney disease; body mass index; obesity; dose-response relationship; epidemiology

## INTRODUCTION

Chronic kidney disease (CKD) is a major public health problem. In Japan, CKD affects 13.3 million adults.<sup>1</sup> With the increasing incidence of hypertension and type 2 diabetes and the aging of the Japanese population, the number of individuals with CKD will likely continue to increase. CKD is recognized as an independent risk factor for myocardial infarction and cardiovascular mortality and can result in significant morbidity, mortality, and increased medical costs.<sup>2</sup>

Obesity is also a major public health issue, and its prevalence has been increasing worldwide. Obesity is

associated with the development of many cardiovascular disease (CVD) risk factors, including type 2 diabetes mellitus,<sup>3,4</sup> hypertension,<sup>5,6</sup> dyslipidemia,<sup>7</sup> and CKD.<sup>8</sup> Prospective cohort studies have revealed the longitudinal relation between body mass index (BMI) and the risk of moderate CKD. A greater baseline BMI was associated with an increased risk of stage  $\geq 3$  CKD in the Physician's Health Study,<sup>9</sup> the Hypertension Detection and Follow-Up Program,<sup>10</sup> and the Framingham Heart Study.<sup>11</sup> Because treatment of long-term CKD is costly, the best approach is to reduce the incidence of stage  $\geq 3$  CKD or prevent it entirely. Examining the modifiable risk factors for stage  $\geq 3$  CKD,

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such as obesity, is important because of the public health implications.

A relationship between obesity and the risk of stage  $\geq 3$  CKD in Japanese participants has been reported.<sup>12</sup> However, not enough information was presented to examine the dose-response relationship between obesity and the risk of CKD (ie obesity was only considered as dichotomous data); consequently, the dose-response relationship in Japanese individuals remains unclear. An examination of the CKD risk using more-detailed BMI categories in a large cohort is warranted. Additionally, no studies have considered the age-specific relationship between BMI and the development of stage  $\geq 3$  CKD. Further research on this issue may help officials implement more effective public health and clinical efforts aimed at the primary prevention of CKD. The purpose of our study was to examine the dose-response relationship between BMI and the development of stage  $\geq 3$  CKD in a general Japanese population.

## METHODS AND PROCEDURES

### Study population

The study population consisted of 194 333 individuals (63 865 men and 130 468 women) aged 40–79 years who were living in Ibaraki Prefecture, Japan. These individuals had participated in community-based annual health checkups in 1993 (as part of the Ibaraki Prefectural Health Study), which were conducted by the local governments in accordance with the Law of Health and Medical Services for the Elderly. The Ibaraki prefectural government collected data from the local governments, and personal information was removed to ensure anonymity. We excluded 18 939 patients (2367 men and 16 572 women) because of incomplete data, 10 075 individuals (4101 men and 5974 women) because of a history of CVD, and 10 491 individuals (3615 men and 6876 women) because of the presence of stage  $\geq 3$  CKD and/or ongoing treatment for CKD. We further excluded 48 864 individuals (17 999 men and 30 865 women) who failed to participate in the 1994 survey, thereby ensuring that all of the participants were followed for at least one year.

Ultimately, the study included 105 611 participants (35 738 men and 69 873 women). These participants were followed by annual examinations until a diagnosis of stage  $\geq 3$  CKD, withdrawal from the repeated examinations, or the end of 2006, whichever occurred first. The Ibaraki Epidemiology Study Union Ethics Review Committee approved the protocol for this cohort study.

### Measurements

Kidney function was assessed using the estimated glomerular filtration rate (eGFR). The eGFR was calculated using the new Japanese abbreviated prediction equation,<sup>13</sup> modified from the Modification of Diet in Renal Disease (MDRD) Study,<sup>14</sup> as recommended by the Japanese Society of Nephrology:

$$\begin{aligned} \text{eGFR (mL/[min}\cdot\text{1.73 m}^2\text{])} \\ = [194 \times (\text{serum creatinine [mg/dL]})]^{-1.094} \\ \times (\text{age})^{-0.287} \times 0.739 \text{ (for women only)} \end{aligned}$$

According to Levey et al, stage  $\geq 3$  CKD is defined as the presence of kidney damage or an eGFR  $< 60$  mL/min/1.73 m<sup>2</sup> reported at least twice in successive annual surveys.<sup>15</sup>

Serum creatinine level was measured using the Jaffe method with an automated analyzer (Hitachi 7350; Hitachi, Tokyo, Japan, or RX-30; Nihon Denshi, Tokyo, Japan) in 1993–2003; in 2004–2006, it was measured using the enzyme method with an automated analyzer (Hitachi 7770; Hitachi). The coefficient of validation for creatinine value was 0.61%. Serum creatinine measurements from 1993–2003 were converted to the value obtained in the enzyme method using the following equation:

$$\begin{aligned} \text{serum creatinine by enzyme method (mg/dL)} \\ = 0.9915 \times \text{serum creatinine by the Jaffe method (mg/dL)} \\ - 0.211 \end{aligned}$$

The serum creatinine values measured using the enzyme method and the serum creatinine values measured using the Jaffe method were then converted to the enzyme method from the same subjects at the same point in time, and the comparability between them was found to be excellent ( $r = 0.99$ ,  $P < 0.001$ ). Proteinuria was defined as a urinary protein excretion of 1+ or more by dipstick test (Ames Hemacombisticks; Bayer-Sankyo Ltd., Tokyo, Japan).

The patients' height in sock feet and weight in light clothing were measured at baseline. BMI was calculated as the weight in kilograms divided by the height in meters squared (kg/m<sup>2</sup>).

We measured the following cardiovascular risk factors: serum total cholesterol, serum high-density-lipoprotein (HDL) cholesterol, serum triglyceride, plasma glucose, blood pressure, use of medications, cigarette smoking, and typical alcohol intake. Blood samples were drawn into two polyethylene terephthalate tubes from seated participants; one tube contained an accelerator, while the other contained sodium fluoride and ethylenediaminetetraacetic acid. Overnight fasting ( $\geq 8$  h) was not mandatory. The serum total cholesterol and serum triglyceride levels were measured using the enzyme method with the RX-30 device in 1993–1995, the H7350 device in 1996–2003, and the H7700 device in 2004–2006. The HDL cholesterol levels were measured using the phosphotungstic acid magnesium method with an MTP-32 device (Corona Electric, Ibaraki, Japan) in 1993–1995, the selective inhibition method with the H7350 device in 1996–2003, and the H7700 device in 2004–2006. Dyslipidemia was defined as triglycerides  $\geq 1.7$  mmol/L, HDL cholesterol  $< 1.036$  mmol/L, or as the patient being prescribed medication for dyslipidemia treatment.

The blood glucose level was measured using the glucose oxidase electrode method with a GA1140 device (Kyoto Daiichi Kagaku, Kyoto, Japan) in 1993–1996, the enzyme method with a H7170 device (Hitachi) in 1997–2003, and

the H7700 device in 1994–2006. The participants were considered diabetic if they had a plasma glucose of  $\geq 6.1$  mmol/L in a fasted state or  $\geq 7.8$  mmol/L in a non-fasted state, or if they were being treated for diabetes mellitus. The laboratory participated in external standardization and successfully met the criteria for precision accuracy for the measurement of blood samples, as established by the Japan Medical Association, the Japanese Association of Medical Technologists, and the Japan Society of Health Evaluation and Promotion.

Blood pressure was measured on the right arm of seated participants who had rested for more than 5 min; trained observers obtained these measurements using a standard mercury sphygmomanometer in 1993–2004 and an automated sphygmomanometer in 2005–2006. When the systolic blood pressure was  $>150$  mm Hg or the diastolic blood pressure was  $>90$  mm Hg, a second measurement was obtained after the subject took several deep breaths. The lower values, which were almost always observed during the second measurement, were used for the analyses. Hypertension was defined as systolic blood pressure  $\geq 140$  mm Hg, diastolic blood pressure  $\geq 90$  mm Hg, or use of antihypertensive medication. CVD risk factors were defined as hypertension, dyslipidemia, and diabetes.

Lastly, we conducted an interview to ascertain the number of cigarettes smoked per day, the typical weekly alcohol intake (converted to grams of ethanol per day), and the history of CVD and CKD.

### Statistical analysis

The participants were classified into the following categories with regard to their BMI ( $\text{kg}/\text{m}^2$ ):  $<18.5$ ; 18.5–20.9; 21.0–22.9; 23.0–24.9; 25.0–26.9; 27.0–29.9; or  $\geq 30.0$ . To compare the participants' physical characteristics according to the BMI categories, one-way analysis of variance was used for continuous variables, and a  $\chi^2$ -test was used for categorical variables. The Cox proportional hazards regression model was used to calculate hazard ratios (HRs) and the 95% confidence intervals (CIs) of risk of development of stage  $\geq 3$  CKD relative to the BMI categories in comparison to the reference group, 21.0–22.9  $\text{kg}/\text{m}^2$ . A BMI of 22  $\text{kg}/\text{m}^2$  is commonly set as the optimal body size in Japan.<sup>16</sup> The analyses were stratified by sex and age groups (40–59 and 60–79 years old).

We used two multivariate-adjusted models. In model one, covariates included age and the potential confounders of cigarette smoking (never, former, current [1–19 cigarettes/day or  $\geq 20$  cigarettes/day]) and typical alcohol intake (never, sometimes, everyday [ $<56$  g/day or  $\geq 56$  g/day]). In model two, potential mediators were added to model one. Potential mediators included systolic blood pressure, the use of antihypertensive medication (yes or no), triglyceride level (log-transformed), serum total cholesterol, serum HDL cholesterol, the use of lipid medication (yes or no), blood glucose status (normal [ $<6.1$  mmol/L in a fasted state or

$<7.8$  mmol/L in a non-fasted state], borderline [6.1–7.0 mmol/L in a fasted state or 7.8–11.1 mmol/L in a non-fasted state], hyperglycemic [ $>7.0$  mmol/L in a fasted state or  $>11.1$  mmol/L in a non-fasted state]), the use of diabetes medication (yes or no), and proteinuria (yes or no). A  $P$  value  $<0.05$  was regarded as statistically significant. The SAS System for Windows, release 9.3 (SAS Institute Inc., Cary, NC, USA), was used for all analyses.

## RESULTS

Sex-stratified baseline characteristics of the cardiovascular risk factors according to our BMI categories are provided in Table 1. All of the factors, except diabetic medication use in men and lipid medication use in men and women, were associated with BMI in both sexes. A higher BMI was linked with a higher eGFR and a higher prevalence of proteinuria in both sexes.

Of the 105 611 participants (35 738 men and 69 873 women), 19 384 (18.4%) developed stage  $\geq 3$  CKD (5978 men and 13 406 women) over a mean follow-up of 5 years (4.9 years for men and 5.1 years for women). Table 2 and Figure show the sex-stratified HRs for the incidence of stage  $\geq 3$  CKD according to BMI category. In both sexes, compared to a BMI of 21.0–22.9  $\text{kg}/\text{m}^2$ , the age- and potential confounder-adjusted HRs were higher for the higher BMI categories (model 1;  $P$  for trend  $<0.001$ ; Table 2). Further, these results were similar even when adjusted for potential mediators (model 2; Figure). The HRs of BMI  $\geq 30.0$   $\text{kg}/\text{m}^2$  were markedly higher in men and women (HR 1.60, 95% CI 1.24–2.06 and HR 1.41, 95% CI 1.25–1.60, respectively).

Table 3 shows the sex-stratified HRs for stage  $\geq 3$  CKD by BMI categories among diabetes-free and CVD risk factor-free patients at baseline. In analyses limited to those free of either diabetes or of any CVD risk factors, the HRs were higher for the higher BMI categories ( $P$  for trend  $<0.001$ ).

Table 4 shows the sex- and age-stratified HRs for the incidence of stage  $\geq 3$  CKD by BMI category compared with a BMI of 21.0–22.9  $\text{kg}/\text{m}^2$ . In men aged 40–59 years, the multivariable HRs of BMI  $\geq 30.0$   $\text{kg}/\text{m}^2$  were significantly higher. In men aged 60–79 years, the multivariable HRs of BMI  $\geq 23.0$   $\text{kg}/\text{m}^2$  were significantly higher. In women aged 40–59 years, the multivariable HRs of the overall BMI categories were not significantly associated ( $P$  for trend = 0.291). In women aged 60–79 years, the multivariable HRs of BMI  $\geq 27.0$   $\text{kg}/\text{m}^2$  were significantly higher. In both sexes and age classes, except women aged 40–59 years, a significant dose-response relationship between BMI and the incidence of stage  $\geq 3$  CKD was observed.

## DISCUSSION

To the best of our knowledge, this is the first cohort study to demonstrate a dose-response relationship between obesity and

**Table 1. Baseline characteristics of participants by BMI categories**

Gender and baseline variables	Body mass index, kg/m <sup>2</sup>							P for difference
	<18.5	18.5–20.9	21.0–22.9	23.0–24.9	25.0–26.9	27.0–29.9	≥30.0	
<b>Men (n = 35 738)</b>								
Number of participants	1570	6717	9044	9097	5928	2899	483	
Age, years	65.0 (8.8)	62.5 (9.5)	60.8 (9.7)	59.8 (9.7)	59.0 (9.6)	58.9 (9.4)	57.4 (9.4)	<0.001
eGFR, mL/(min·1.73 m <sup>2</sup> )	89.9 (18.6)	90.2 (18.4)	88.6 (17.4)	87.1 (17.3)	86.4 (16.8)	85.3 (16.5)	84.4 (16.6)	<0.001
Proteinuria, %	2.2	1.7	1.4	1.8	2.2	3.7	6.4	<0.001
Total cholesterol, mmol/L	4.67 (0.81)	4.75 (0.82)	4.94 (0.85)	5.07 (0.86)	5.17 (0.86)	5.21 (0.86)	5.26 (0.86)	<0.001
HDL cholesterol, mmol/L	1.63 (0.43)	1.52 (0.40)	1.41 (0.38)	1.30 (0.34)	1.24 (0.31)	1.18 (0.29)	1.14 (0.28)	<0.001
Triacylglycerol, mmol/L	1.06 (0.59)	1.21 (0.71)	1.50 (0.91)	1.78 (1.05)	2.05 (1.22)	2.23 (1.31)	2.32 (1.31)	<0.001
Blood glucose, mmol/L	6.41 (2.15)	6.37 (2.09)	6.35 (1.98)	6.39 (2.03)	6.45 (2.01)	6.60 (2.26)	6.70 (2.23)	<0.001
Systolic blood pressure, mm Hg	131.4 (18.2)	133.5 (17.7)	135.1 (16.9)	136.9 (16.6)	138.2 (16.2)	140.8 (16.7)	142.6 (16.2)	<0.001
Diastolic blood pressure, mm Hg	76.9 (10.6)	78.1 (10.4)	79.7 (10.3)	81.3 (10.3)	82.9 (10.3)	84.6 (10.6)	86.9 (10.9)	<0.001
Lipid medication use, %	0.4	0.7	1.2	1.6	1.5	2.0	2.3	0.289
Diabetic medication use, %	3.2	2.6	2.7	3.6	3.7	4.0	3.1	0.361
Antihypertensive medication use, %	12.5	14.5	16.6	19.7	22.4	26.5	32.1	<0.001
Smoking status, %								<0.001
Never	18.1	18.7	22.3	24.1	24.4	25.1	28.6	
Former	22.2	23.5	27.3	30.3	32.0	33.3	28.8	
Current								
<20 cigarettes/day	26.4	21.0	16.2	13.8	12.0	10.7	9.7	
≥20 cigarettes/day	33.3	36.8	34.2	31.9	31.6	31.0	32.9	
Alcohol intake, %								<0.001
Never	44.8	35.6	31.9	31.1	31.0	33.4	37.7	
Sometimes	10.4	11.1	11.9	13.8	14.6	15.7	14.9	
Everyday								
<56 g/day	41.1	47.5	49.5	49.1	47.3	42.9	38.9	
≥56 g/day	3.6	5.8	6.7	6.1	7.1	8.1	8.5	
<b>Women (n = 69 873)</b>								
Number of participants	2846	12 052	17 146	17 122	11 559	7229	1919	
Age, years	60.4 (10.3)	57.5 (9.8)	57.8 (9.3)	58.5 (8.8)	59.4 (8.6)	59.8 (8.4)	59.0 (8.5)	<0.001
eGFR, mL/(min·1.73 m <sup>2</sup> )	94.5 (22.0)	96.1 (22.3)	94.2 (21.1)	93.4 (24.9)	91.8 (20.7)	91.4 (20.4)	91.3 (21.0)	<0.001
Proteinuria, %	0.9	0.7	0.8	0.9	1.2	1.7	3.3	<0.001
Total cholesterol, mmol/L	5.19 (0.88)	5.27 (0.87)	5.39 (0.89)	5.48 (0.89)	5.55 (0.88)	5.60 (0.91)	5.61 (0.92)	<0.001
HDL cholesterol, mmol/L	1.72 (0.40)	1.61 (0.38)	1.51 (0.36)	1.43 (0.34)	1.38 (0.33)	1.35 (0.31)	1.33 (0.31)	<0.001
Triacylglycerol, mmol/L	1.07 (0.50)	1.23 (0.65)	1.42 (0.79)	1.61 (0.90)	1.77 (0.96)	1.88 (1.04)	1.94 (0.99)	<0.001
Blood glucose, mmol/L	5.90 (1.61)	5.79 (1.40)	5.83 (1.40)	5.96 (1.50)	6.04 (1.52)	6.16 (1.71)	6.35 (2.03)	<0.001
Systolic blood pressure, mm Hg	126.5 (17.9)	127.2 (17.3)	130.1 (17.0)	132.7 (16.9)	135.4 (16.6)	138.6 (16.8)	141.7 (16.9)	<0.001
Diastolic blood pressure, mm Hg	73.5 (10.4)	74.7 (10.3)	76.4 (10.1)	78.3 (10.0)	79.9 (10.0)	82.0 (10.0)	84.1 (10.6)	<0.001
Lipid medication use, %	1.9	2.2	3.2	3.8	4.2	4.6	4.6	0.988
Diabetic medication use, %	1.3	1.5	1.5	1.9	2.3	2.7	3.2	<0.001
Antihypertensive medication use, %	8.7	10.4	13.8	19.0	23.9	30.6	38.0	<0.001
Smoking status, %								<0.001
Never	92.2	95.1	95.5	95.9	95.7	95.2	93.3	
Former	0.5	0.4	0.6	0.5	0.6	0.7	0.8	
Current								
<20 cigarettes/day	4.9	3.2	2.7	2.4	2.5	2.7	3.9	
≥20 cigarettes/day	2.3	1.3	1.1	1.3	1.3	1.5	2.1	
Alcohol intake, %								<0.001
Never	91.3	90.0	90.0	90.7	90.8	91.7	91.5	
Sometimes	4.8	5.8	6.3	5.7	5.9	5.1	4.8	
Everyday								
<56 g/day	3.9	4.1	3.6	3.5	3.2	3.1	3.4	
≥56 g/day	—	0.1	0.1	0.1	0.1	0.1	0.3	

BMI, body mass index; eGFR, estimated glomerular filtration rate; HDL, high-density lipoprotein; SD, standard deviation.

Showing mean (SD) for continuous variables: age, fasting and non-fasting blood glucose, systolic and diastolic blood pressure, total cholesterol, HDL cholesterol, and triglycerides.

SI conversion factors: to convert blood glucose values to mmol/L, multiply by 0.05551; to convert cholesterol values to mmol/L, multiply by 0.02586; to convert triglycerides values to mmol/L, multiply by 0.01129.

the risk of stage  $\geq 3$  CKD in a Japanese population. The dose-response relationship was found in men aged 40–59 and 60–79 years and in women aged 60–79 years. In addition, this relationship was independent of diabetes and other CVD risk factors (ie hypertension and dyslipidemia). We also observed that the risk of stage  $\geq 3$  CKD was markedly higher in obese

men and women with a BMI  $\geq 30.0$  kg/m<sup>2</sup> than in men and women with a BMI of 21.0–22.9 kg/m<sup>2</sup>, except in women aged 40–59 years.

The significant relationship observed between BMI and the incidence of stage  $\geq 3$  CKD in our study was consistent with that observed in previous studies in Caucasian and Asian

**Table 2. Sex-specific HRs and 95% CI for stage  $\geq 3$  CKD by BMI categories**

Sex and body mass index category (kg/m <sup>2</sup> )	Number of participants	Number of person-years	Incidence rates per 1000 person-years	Age-adjusted HR	95% CI	Multivariate-adjusted HR <sup>a</sup> (model 1)	95% CI	P for trend
<b>Men</b>								
<18.5	1570	7061	20.1	<b>0.76</b>	<b>0.63, 0.90</b>	<b>0.73</b>	<b>0.69, 0.61</b>	<0.001
18.5–20.9	6717	33677	20.1	<b>0.90</b>	<b>0.82, 0.99</b>	<b>0.89</b>	<b>0.87, 0.81</b>	
21.0–22.9	9044	47022	19.9	1	(ref.)	1	(ref.)	
23.0–24.9	9097	46973	23.1	<b>1.27</b>	<b>1.16, 1.38</b>	<b>1.27</b>	<b>1.09, 1.17</b>	
25.0–26.9	5928	30170	22.9	<b>1.38</b>	<b>1.25, 1.52</b>	<b>1.39</b>	<b>1.11, 1.26</b>	
27.0–29.9	2899	14091	23.6	<b>1.48</b>	<b>1.31, 1.68</b>	<b>1.48</b>	<b>1.08, 1.30</b>	
$\geq 30.0$	483	2252	28.4	<b>2.01</b>	<b>1.56, 2.59</b>	<b>1.98</b>	<b>1.24, 1.54</b>	
<b>Women</b>								
<18.5	2846	14223	19.8	<b>0.75</b>	<b>0.66, 0.85</b>	<b>0.74</b>	<b>0.72, 0.66</b>	<0.001
18.5–20.9	12052	65680	17.8	<b>0.86</b>	<b>0.80, 0.93</b>	<b>0.86</b>	<b>0.84, 0.80</b>	
21.0–22.9	17146	94954	20.1	1	(ref.)	1	(ref.)	
23.0–24.9	17122	92420	22.0	1.05	0.99, 1.12	1.05	0.95, 0.99	
25.0–26.9	11559	61186	24.7	<b>1.11</b>	<b>1.04, 1.19</b>	1.11	0.96, 1.04	
27.0–29.9	7229	36348	27.9	<b>1.23</b>	<b>1.14, 1.33</b>	<b>1.23</b>	<b>1.01, 1.14</b>	
$\geq 30.0$	1919	8760	34.5	<b>1.66</b>	<b>1.47, 1.87</b>	<b>1.64</b>	<b>1.25, 1.45</b>	

BMI, body mass index; CI, confidence interval; CKD, chronic kidney disease; HR, hazard ratio.

<sup>a</sup>Adjusted for age (years), smoking status (never, ex-, current <20 cigarettes/day, or  $\geq 20$  cigarettes/day), and alcohol intake (never, sometimes, <56 g/day, or  $\geq 56$  g/day).

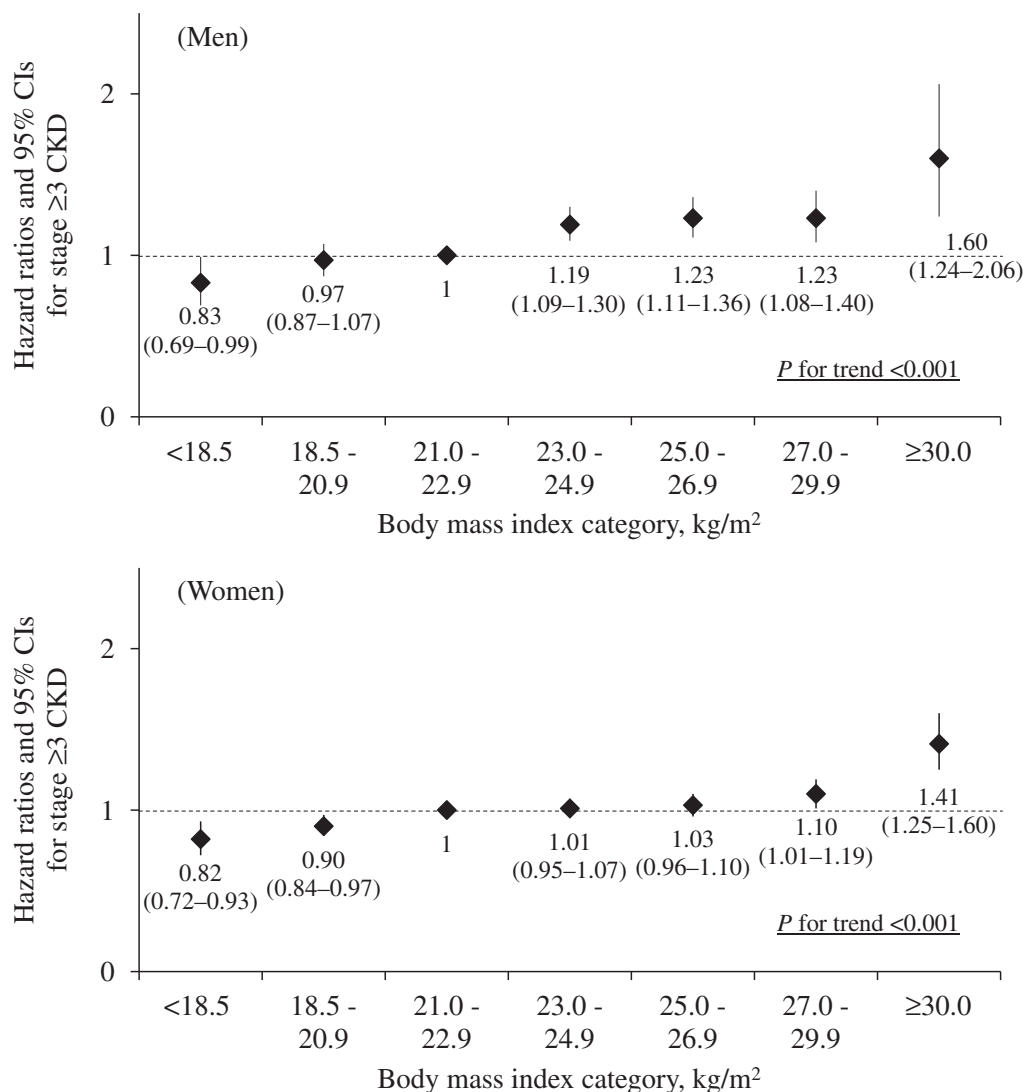


Figure. The multivariable-adjusted hazard ratios (HRs) and 95% confidence intervals (CIs) for the development of stage  $\geq 3$  chronic kidney disease (CKD) in men and women.

**Table 3. Sex-specific HRs and 95% CIs for stage  $\geq 3$  CKD by BMI categories among diabetes-free and CVD risk factor-free at baseline**

Sex and body mass index category (kg/m <sup>2</sup> )	Number of subjects	Number of person-years	Incidence rates per 1000 person-years	Age-adjusted HR	95% CI	Multivariable HR <sup>c</sup>	95% CI	<i>P</i> for trend
<b>Diabetes<sup>a</sup>-free</b>								
<b>Men</b>								
<18.5	1207	5426	19.5	<b>0.73</b>	<b>0.60, 0.90</b>	<b>0.80</b>	<b>0.65, 0.99</b>	<0.001
18.5–20.9	5352	26978	19.4	<b>0.89</b>	<b>0.79, 0.99</b>	0.94	0.84, 1.05	
21.0–22.9	7247	38202	19.9	1	(ref.)	1	(ref.)	
23.0–24.9	7255	37952	23.1	<b>1.27</b>	<b>1.15, 1.40</b>	<b>1.21</b>	<b>1.09, 1.33</b>	
25.0–26.9	4601	23495	23.0	<b>1.38</b>	<b>1.24, 1.55</b>	<b>1.26</b>	<b>1.12, 1.41</b>	
27.0–29.9	2227	11013	22.2	<b>1.44</b>	<b>1.25, 1.67</b>	<b>1.24</b>	<b>1.07, 1.44</b>	
>30.0	359	1715	29.2	<b>2.02</b>	<b>1.52, 2.69</b>	<b>1.64</b>	<b>1.23, 2.19</b>	
<b>Women</b>								
<18.5	2492	12512	19.4	<b>0.75</b>	<b>0.65, 0.86</b>	<b>0.80</b>	<b>0.70, 0.92</b>	<0.001
18.5–20.9	10818	58756	17.3	<b>0.86</b>	<b>0.79, 0.93</b>	<b>0.89</b>	<b>0.82, 0.96</b>	
21.0–22.9	15336	85182	19.8	1	(ref.)	1	(ref.)	
23.0–24.9	15086	81737	21.4	1.03	0.97, 1.11	1.00	0.93, 1.06	
25.0–26.9	10024	53502	24.4	<b>1.11</b>	<b>1.03, 1.19</b>	1.04	0.96, 1.11	
27.0–29.9	6182	31475	27.2	<b>1.21</b>	<b>1.12, 1.32</b>	<b>1.09</b>	<b>1.00, 1.18</b>	
>30.0	1574	7272	33.7	<b>1.65</b>	<b>1.44, 1.89</b>	<b>1.41</b>	<b>1.23, 1.62</b>	
<b>CVD risk factor<sup>b</sup>-free</b>								
<b>Men</b>								
<18.5	501	2364	11.8	<b>0.63</b>	<b>0.42, 0.95</b>	<b>0.64</b>	<b>0.42, 0.96</b>	<0.001
18.5–20.9	1815	9989	12.0	0.83	0.65, 1.06	0.84	0.65, 1.08	
21.0–22.9	1945	10918	12.4	1	(ref.)	1	(ref.)	
23.0–24.9	1528	8402	13.9	<b>1.29</b>	<b>1.01, 1.65</b>	<b>1.30</b>	<b>1.01, 1.67</b>	
25.0–26.9	757	4007	12.5	1.36	0.98, 1.88	1.30	0.93, 1.81	
27.0–29.9	232	1121	16.1	<b>1.85</b>	<b>1.13, 3.03</b>	<b>1.78</b>	<b>1.08, 2.93</b>	
>30.0	29	109	9.2	2.20	0.31, 15.75	1.94	0.27, 13.92	
<b>Women</b>								
<18.5	1304	6802	15.1	0.90	0.72, 1.12	0.92	0.74, 1.15	<0.001
18.5–20.9	5285	29349	12.0	0.99	0.86, 1.14	1.01	0.87, 1.16	
21.0–22.9	6243	36399	11.8	1	(ref.)	1	(ref.)	
23.0–24.9	4920	27907	14.0	<b>1.17</b>	<b>1.02, 1.34</b>	<b>1.16</b>	<b>1.01, 1.33</b>	
25.0–26.9	2509	14196	16.3	<b>1.27</b>	<b>1.08, 1.49</b>	<b>1.21</b>	<b>1.03, 1.42</b>	
27.0–29.9	1126	5989	19.2	<b>1.57</b>	<b>1.27, 1.92</b>	<b>1.47</b>	<b>1.2, 1.81</b>	
>30.0	222	1111	26.1	<b>2.15</b>	<b>1.47, 3.13</b>	<b>1.98</b>	<b>1.35, 2.89</b>	

BMI, body mass index; CI, confidence interval; CKD, chronic kidney disease; CVD, cardiovascular disease; HR, hazard ratio.

<sup>a</sup>Diabetes is defined as plasma glucose  $\geq 6.1$  mmol/L in a fasted state or  $\geq 7.8$  mmol/L in a non-fasted state, or being treated for diabetes mellitus.

<sup>b</sup>Cardiovascular disease risk factors are hypertension, dyslipidemia, and diabetes.

<sup>c</sup>Adjusted for age (years), systolic blood pressure (mm Hg), total cholesterol level (mmol/liter), high-density lipoprotein cholesterol level (mmol/liter), log-transformed triglyceride level (mmol/liter), proteinuria (yes or no), smoking status (never, ex-, current <20 cigarettes/day, or  $\geq 20$  cigarettes/day), and alcohol intake (never, sometimes, <56 g/day, or  $\geq 56$  g/day).

populations.<sup>11,17,18</sup> The Framingham Offspring Study, which included 2585 participants (mean age, 43 years) who were followed from 1978–2001 (mean follow-up, 18.5 years), showed a strong dose-response relationship between baseline BMI and risk of CKD (defined as eGFR using the MDRD Study equation:  $\leq 64.25$  mL/[min $\cdot 1.73$  m<sup>2</sup>] in men and  $\leq 59.25$  mL/[min $\cdot 1.73$  m<sup>2</sup>] in women).<sup>11</sup> The multivariable odds ratio of CKD was 1.23 (95% CI, 1.08–1.41) per one standard deviation of approximately 4 kg.<sup>11</sup> A Japanese community-based study, which followed 100 753 individuals (mean age, 49 years) for 17 years, revealed that a higher BMI at baseline was associated with an increased risk of end-stage renal disease in men but not women.<sup>18</sup> The multivariable-adjusted odds ratios of end-stage renal disease were 1.27 (95% CI, 1.21–1.45) in men and 0.95 (95% CI, 0.83–1.09) in women for each 2 kg/m<sup>2</sup> increment of BMI.<sup>18</sup> Although these

authors did not examine the association between BMI and the risk of CKD among older adults, their results in middle-aged adults are consistent with our findings.

The association between obesity and stage  $\geq 3$  CKD may be mediated through multiple biological mechanisms, including hormonal factors, inflammation, oxidative stress, and endothelial dysfunction.<sup>19,20</sup> In obese individuals, the rennin-angiotensin-aldosterone system is commonly activated,<sup>21</sup> and it is a well-coordinated hormonal system that regulates adrenal, cardiovascular, and kidney function by controlling the fluid and electrolyte balance. Activation of this system leads to the development of hypertension via the production of angiotensin 2, which causes further damage to the kidneys.<sup>22</sup> Estrogen, a sex hormone that is secreted more in premenopausal women compared with men and postmenopausal women, decreases the expression of angiotensin

**Table 4. Age and sex-specific HRs and 95% CIs for stage  $\geq 3$  CKD by BMI categories**

Sex, age group, and BMI categories (kg/m <sup>2</sup> )	Number of participants	Number of person-years	Incidence rates per 1000 person-years	Age-adjusted HR	95% CI	Multivariable HR <sup>a</sup>	95% CI	P for trend
<b>Men</b>								
Age 40–59 years								
<18.5	298	1373	2.9	0.44	0.16, 1.18	0.47	0.17, 1.28	
18.5–20.9	1948	10900	4.3	<b>0.63</b>	<b>0.45, 0.88</b>	<b>0.71</b>	<b>0.50, 0.99</b>	
21.0–22.9	3310	18 194	6.7	1	(ref.)	1	(ref.)	
23.0–24.9	3762	20 086	9.4	<b>1.41</b>	<b>1.12, 1.77</b>	1.22	0.97, 1.54	0.001
25.0–26.9	2676	14 323	8.9	<b>1.34</b>	<b>1.05, 1.72</b>	1.10	0.85, 1.42	
27.0–29.9	1384	7 130	10.9	<b>1.57</b>	<b>1.18, 2.09</b>	1.21	0.90, 1.63	
$\geq 30.0$	264	1241	16.9	<b>2.59</b>	<b>1.63, 4.11</b>	<b>1.83</b>	<b>1.14, 2.95</b>	
Age 60–79 years								
<18.5	1272	5688	24.3	<b>0.77</b>	<b>0.64, 0.92</b>	0.84	0.70, 1.01	
18.5–20.9	4769	22 777	27.7	0.93	0.84, 1.03	0.99	0.89, 1.10	
21.0–22.9	5734	28 828	28.3	1	(ref.)	1	(ref.)	
23.0–24.9	5335	26 887	33.4	<b>1.25</b>	<b>1.13, 1.37</b>	<b>1.18</b>	<b>1.07, 1.30</b>	<0.001
25.0–26.9	3252	15 847	35.5	<b>1.39</b>	<b>1.25, 1.55</b>	<b>1.26</b>	<b>1.13, 1.41</b>	
27.0–29.9	1515	6961	36.6	<b>1.46</b>	<b>1.27, 1.68</b>	<b>1.22</b>	<b>1.06, 1.41</b>	
$\geq 30.0$	219	1011	42.5	<b>1.83</b>	<b>1.34, 2.48</b>	<b>1.47</b>	<b>1.08, 2.01</b>	
<b>Women</b>								
Age 40–59 years								
<18.5	1209	6864	6.8	0.91	0.68, 1.23	0.98	0.72, 1.33	
18.5–20.9	6611	38 770	6.7	0.91	0.78, 1.07	0.96	0.82, 1.12	
21.0–22.9	9324	56 401	7.7	1	(ref.)	1	(ref.)	
23.0–24.9	8808	51 514	8.4	1.04	0.91, 1.19	1.00	0.88, 1.15	0.291
25.0–26.9	5436	31 685	9.2	1.10	0.95, 1.28	1.02	0.87, 1.18	
27.0–29.9	3219	17 926	9.5	1.17	0.98, 1.39	1.02	0.85, 1.22	
$\geq 30.0$	928	4778	11.3	<b>1.46</b>	<b>1.10, 1.94</b>	1.19	0.90, 1.59	
Age 60–79 years								
<18.5	1637	7359	31.9	<b>0.75</b>	<b>0.65, 0.86</b>	<b>0.81</b>	<b>0.70, 0.93</b>	
18.5–20.9	5441	26 910	33.9	<b>0.86</b>	<b>0.79, 0.93</b>	<b>0.89</b>	<b>0.82, 0.97</b>	
21.0–22.9	7822	38 553	38.3	1	(ref.)	1	(ref.)	
23.0–24.9	8314	40 906	39.1	1.04	0.97, 1.12	1.00	0.93, 1.07	<0.001
25.0–26.9	6123	29 501	41.4	<b>1.09</b>	<b>1.01, 1.18</b>	1.02	0.95, 1.10	
27.0–29.9	4010	18 422	45.8	<b>1.22</b>	<b>1.12, 1.33</b>	<b>1.10</b>	<b>1.00, 1.19</b>	
$\geq 30.0$	991	3982	62.3	<b>1.67</b>	<b>1.46, 1.90</b>	<b>1.44</b>	<b>1.26, 1.65</b>	

BMI, body mass index; CI, confidence interval; CKD, chronic kidney disease; HR, hazard ratio.

<sup>a</sup>Adjusted for age (years), smoking status (never, ex-, current <20 cigarettes/day, or  $\geq 20$  cigarettes/day), alcohol intake (never, sometimes, <56 g/day, or  $\geq 56$  g/day), fasting status (yes or no), systolic blood pressure (mm Hg), antihypertensive medication use (yes or no), total cholesterol level (mmol/liter), high-density lipoprotein cholesterol level (mmol/liter), log-transformed triglyceride level (mmol/liter), lipid medication use (yes or no), blood glucose status (normal: <6.1 mmol/l during fasting or <7.8 mmol/l during nonfasting; border: 6.1–7.0 mmol/l during fasting or 7.8–11.1 mmol/l during nonfasting; hyperglycemic: 7.0 mmol/l during fasting or 11.1 mmol/l during nonfasting), diabetes medication use (yes or no), and proteinuria (yes or no).

type 1 receptors in the vasculature and kidneys<sup>23</sup> and reduces the expression and activity of angiotensin-converting enzymes.<sup>24,25</sup> These biological mechanisms may be underlying factors for the significant relationship between obesity and the development of stage  $\geq 3$  CKD among middle-aged women in our study.

The strength of our study is that stage  $\geq 3$  CKD was defined as an eGFR level <60 mL/min/1.73 m<sup>2</sup> reported at more than two successive annual surveys. Further, all of the blood samples were measured by the same laboratory, which was verified using a validated quality control system.<sup>26</sup> However, there are several limitations. First, we only examined generalized obesity and not abdominal obesity, because the measurements of central obesity were not available during the baseline examination. Second, potential residual confounders

may not have been assessed, such as fat distribution, dietary lifestyle (ie protein and salt intake), and physical activity. Third, detailed information on use of medications such as statins and omega 3-fatty acids was not collected because of the nature of the community-based health checkup.

Obesity was associated with the risk of developing stage  $\geq 3$  CKD among men and older women. Compared with participants who had a normal BMI (21.0–22.9 kg/m<sup>2</sup>), those with a BMI  $\geq 30.0$  kg/m<sup>2</sup> had a markedly high risk of developing stage  $\geq 3$  CKD. Weight management may be important for preventing CKD in obese men and women.

## ONLINE ONLY MATERIAL

Abstract in Japanese.

## ACKNOWLEDGEMENT

This research was supported by a Grant-in-Aid from the Ministry of Health, Labor and Welfare, Health and Labor Sciences Research Grants, Japan (Research on Health Services: H17-Kenkou-007; Comprehensive Research on Cardiovascular and Life-Style Related Diseases: H18-Junkankitou[Seishuu]-Ippan-012; Comprehensive Research on Cardiovascular and Life-Style Related Diseases: H20-Junkankitou[Seishuu]-Ippan-013; Intractable Diseases Conquest Research: H21-Nanchi-Ippan-059; and Comprehensive Research on Cardiovascular and Life-Style Related Diseases: H23-Junkankitou[Seishuu]-Ippan-005).

Conflicts of interest: None declared.

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